Complement Regulator FHR-3 Is Elevated either Locally or Systemically in a Selection of Autoimmune Diseases.

Schäfer N, Grosche A, Reinders J, Hauck SM, Pouw RB, Kuijpers TW, Wouters D, Ehrenstein B, Enzmann V, Zipfel PF, Skerka C, Pauly D (2016) Complement Regulator FHR-3 Is Elevated either Locally or Systemically in a Selection of Autoimmune Diseases. *Front Immunol* 7, 542.

Abstract

The human complement factor H-related protein-3 (FHR-3) is a soluble regulator of the complement system. Homozygous cfhr3/1 deletion is a genetic risk factor for the autoimmune form of atypical hemolytic-uremic syndrome (aHUS), while also found to be protective in age-related macular degeneration (AMD). The precise function of FHR-3 remains to be fully characterized. We generated four mouse monoclonal antibodies (mAbs) for FHR-3 (RETC) without cross-reactivity to the complement factor H (FH)-family. These antibodies detected FHR-3 from human serum with a mean concentration of 1 µg/mL. FHR-3 levels in patients were significantly increased in sera from systemic lupus erythematosus, rheumatoid arthritis, and polymyalgia rheumatica but remained almost unchanged in samples from AMD or aHUS patients. Moreover, by immunostaining of an aged human donor retina, we discovered a local FHR-3 production by microglia/macrophages. The mAb RETC-2 modulated FHR-3 binding to C3b but not the binding of FHR-3 to heparin. Interestingly, FHR-3 competed with FH for binding C3b and the mAb RETC-2 reduced the interaction of FHR-3 and C3b, resulting in increased FH binding. Our results unveil a previously

unknown systemic involvement of FHR-3 in rheumatoid diseases and a putative local role of FHR-3 mediated by microglia/macrophages in the damaged retina. We conclude that the local FHR-3/FH equilibrium in AMD is a potential therapeutic target, which can be modulated by our specific mAb RETC-2.

Beteiligte Forschungseinheiten

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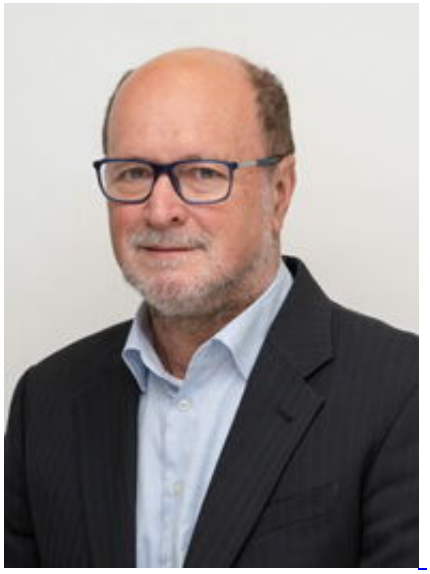
Details



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